SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Vyloy 300 mg powder for concentrate for solution for infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains an extractable amount of 300 mg zolbetuximab.

After reconstitution, each mL of solution contains 20 mg of zolbetuximab.

Zolbetuximab is manufactured from genetically modified CHO (Chinese Hamster Ovary) cells.

Excipient with known effect

Each mL of concentrate contains 0.21 mg of polysorbate 80.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion.

White to off-white lyophilised powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vyloy, in combination with fluoropyrimidine- and platinum-containing chemotherapy, is indicated for the first-line treatment of adult patients with locally advanced unresectable or metastatic human epidermal growth factor

receptor 2 (HER2)-negative gastric or gastro-oesophageal junction (GEJ) adenocarcinoma whose tumours are Claudin (CLDN) 18.2 positive (see section 5.1).

4.2 Posology and method of administration

Treatment with Vyloy should be initiated and supervised by a physician experienced in the use of anticancer therapies.

Posology

Patient selection
Select patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 immunohistochemical staining) as determined by a validated test, for treatment with Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).

Prior to administration
If a patient is experiencing nausea and/or vomiting prior to administration of Vyloy, the symptoms should be resolved to Grade ≤1 before administering the first infusion.

Recommended pre-treatment
Prior to each infusion of Vyloy, premedicate patients with a combination of antiemetics (e.g., NK-1 receptor blockers and/or 5-HT3 receptor blockers, as well as other medicinal products as indicated), for the prevention of nausea and vomiting (see section 4.4).

Recommended dose
Table 1. Recommended Vyloy dosage based on body surface area

Single loading dose	Maintenance doses	Duration of therapy
800 mg/m^2 intravenously, Cycle 1, Day 1[a] Administer Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).[b]	600 mg/m^2 intravenously every 3 weeks or 400 mg/m^2 intravenously every 2 weeks[c] Administer Vyloy in combination with fluoropyrimidine- and platinum-containing chemotherapy (see section 5.1).[b]	Until disease progression or unacceptable toxicity.

a. The cycle duration of Vyloy is determined based on the respective chemotherapy backbone (see section 5.1).
b. Refer to the fluoropyrimidine- or platinum-containing chemotherapy prescribing information regarding the dosing information for chemotherapy.
c. Based on pharmacokinetic modelling exercise (see section 5.2).

Dose modifications

No dose reduction for Vyloy is recommended. Adverse reactions for Vyloy are managed by infusion rate reduction, interruption, and/or discontinuation as presented in Table 2.

Table 2. Dose modifications for Vyloy

Adverse reaction	Severity[a]	Dose modification
Hypersensitivity reactions (see section 4.4)	Anaphylactic reaction, suspected anaphylaxis, Grade 3 or 4	Immediately stop the infusion and permanently discontinue.
	Grade 2	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. • For the next infusion, premedicate and administer per the infusion rates in Table 3.
Infusion related reaction (see section 4.4)	Grade 3 or 4	Immediately stop the infusion and permanently discontinue.

Adverse reaction	Severity[a]	Dose modification
	Grade 2	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. • For the next infusion, premedicate and administer per the infusion rates in Table 3.
Nausea (see section 4.4)	Grade 2 or 3	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. • For the next infusion, administer per the infusion rates in Table 3.
Vomiting (see section 4.4)	Grade 4	Permanently discontinue.
	Grade 2 or 3	• Interrupt the infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. • For the next infusion, administer per the infusion rates in Table 3.

a. Toxicity was graded per National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.03 (NCI-CTCAE v4.03) where Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening.

Special populations

Elderly
No dose adjustment is required in patients ≥65 years of age (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (see section 5.2). Vyloy has only been evaluated in a limited number of patients with severe renal impairment.

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (see section 5.2). Vyloy has only been evaluated in a limited number of patients with moderate hepatic impairment and has not been evaluated in patients with severe hepatic impairment.

Paediatric population

The safety and efficacy of Vyloy in the paediatric population have not been established.

Method of administration

Vyloy is for intravenous use. The recommended dose is administered by intravenous infusion over a minimum of 2 hours. Vyloy must not be administered as an intravenous push or bolus injection.

If Vyloy and fluoropyrimidine- and platinum-containing chemotherapy are administered on the same day, Vyloy must be administered first.

To help minimise potential adverse reactions, it is recommended that each infusion should be started at a slower rate than the initially calculated rate for the entire infusion, and gradually increased as tolerated during the course of the infusion (see Table 3).

If the infusion time exceeds the recommended storage time at room temperature (8 hours from end of preparation of infusion solution), the infusion bag must be discarded and a new infusion bag prepared to continue the infusion (see section 6.3 for recommended storage times).

Table 3. Infusion rates recommended for each Vyloy infusion

Vyloy dose		**Infusion Rate**	
		First 30-60 minutes	**Remaining infusion time[b]**
Single loading dose (Cycle 1, Day 1)[a]	800 mg/m^2	100 mg/m^2/hr	200-400 mg/m^2/hr
Maintenance doses	600 mg/m^2 every 3 weeks or 400 mg/m^2 every 2 weeks	75 mg/m^2/hr or 50 mg/m^2/hr	150-300 mg/m^2/hr or 100-200 mg/m^2/hr

a. The cycle duration of Vyloy is determined based on the respective chemotherapy backbone (see section 5.1).
b. In the absence of adverse reactions after 30-60 minutes, the infusion rate can be increased as tolerated.

For instructions on reconstitution and dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity reactions
Hypersensitivity reactions in patients treated with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy during clinical studies were characterised by anaphylactic reactions and drug hypersensitivity (see section 4.8).

Monitor patients during and after infusion with Vyloy (at least 2 hours, or longer if clinically indicated) for hypersensitivity reactions with symptoms and signs that are highly suggestive of anaphylaxis (urticaria, repetitive cough, wheeze and throat tightness/change in voice).

If an anaphylactic reaction occurs, administration of Vyloy should be immediately and permanently discontinued and appropriate medical therapy administered.

For any Grade 3 or 4 hypersensitivity reaction or hypersensitivity reaction with features of anaphylaxis, administration of Vyloy should be immediately and permanently discontinued and appropriate medical therapy instituted based on the type of reaction.

For any Grade 2 hypersensitivity reaction, interrupt the Vyloy infusion until Grade ≤1, then resume the infusion at a reduced infusion rate for the remaining infusion. Pre-medicate the patient with antihistamines for the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of a hypersensitivity reaction. The infusion rate may be gradually increased as tolerated (see section 4.2).

Infusion-related reaction
Infusion-related reaction (IRR) has occurred during clinical studies with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy (see section 4.8).
Monitor patients for signs and symptoms of infusion-related reaction including nausea, vomiting, abdominal pain, salivary hypersecretion, pyrexia, chest discomfort, chills, back pain, cough and hypertension. These signs and symptoms are usually reversible with the interruption of the infusion.
For Grade 3 or 4 IRRs, administration of Vyloy should be immediately and permanently discontinued and appropriate medical therapy instituted.
For Grade 2 IRRs, interrupt the Vyloy infusion until Grade ≤1, then resume the infusion at a reduced infusion rate for the remaining infusion. Pre-medicate the patient with antihistamines for the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of an IRR. The infusion rate may be gradually increased as tolerated (see section 4.2).
Nausea and vomiting
During clinical studies, nausea and vomiting were the most frequently observed gastrointestinal adverse reactions with Vyloy in combination with

fluoropyrimidine and platinum-containing chemotherapy treatment (see section 4.8).
Nausea and vomiting occurred more often during the first cycle of treatment but decreased in incidence with subsequent cycles of treatment.
To prevent nausea and vomiting, pre-treatment with antiemetics is recommended prior to each infusion of Vyloy (see section 4.2).
During and after infusion, patients should be monitored and managed using standard of care, including antiemetics or fluid replacement, as clinically indicated.
For Grade 4 vomiting, permanently discontinue treatment with Vyloy.
For Grade 2 or 3 nausea or vomiting, interrupt the Vyloy infusion until Grade ≤1, then resume at a reduced infusion rate for the remaining infusion. For the next infusion, administer per the infusion rates in Table 3, and closely monitor the patient for symptoms and signs of nausea or vomiting. The infusion rate may be gradually increased as tolerated (see section 4.2).

Excipient information
This medicinal product contains 3.15 mg of polysorbate 80 in each vial. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No *in vitro* or *in vivo* drug-drug interaction or transporter studies have been conducted (see section 5.2).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of zolbetuximab in pregnant women. No adverse effects were observed in an animal reproductive and developmental study with intravenous administration of zolbetuximab to pregnant mice during organogenesis. Based on AUC, the doses administered in this study were up to approximately 1.8 times higher than human exposure at the recommended therapeutic dose of 600 mg/m^2 (see section 5.3). Vyloy should only be given to a pregnant woman if the benefit outweighs the potential risk.

Breastfeeding

There are no data on the presence of zolbetuximab in human milk, the effects on the breastfed child, or the effects on milk production. Because many drugs, including antibodies are excreted in human milk and because of the potential for serious adverse reactions in a breastfed child, breastfeeding is not recommended during treatment with Vyloy.

Fertility

Studies to evaluate the effect of zolbetuximab on fertility have not been performed. Thus, the effect of Vyloy on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

No studies with Vyloy and the effects on the ability to drive or use machines have been performed. Based on reported adverse reactions, Vyloy may influence the ability to drive and use machines. Caution should be exercised when driving or operating machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of Vyloy was evaluated in the integrated safety population from two phase 2 studies (FAST, ILUSTRO) and two phase 3 studies (SPOTLIGHT, GLOW) in 631 patients who received at least one dose of Vyloy 800 mg/m^2 as a loading dose followed by 600 mg/m^2 maintenance doses every 3 weeks in combination with fluoropyrimidine and platinum-containing chemotherapy. The median duration of exposure to zolbetuximab was 174 days (range: 1 to 1791 days).

Serious adverse events occurred in 45% of patients treated with Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy. The most common serious adverse reactions (≥2%) were vomiting (6.8%) and nausea (4.9%).

Thirty-seven percent of patients permanently discontinued Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy for adverse events; the most common adverse reactions (≥2%) leading to dose discontinuation were vomiting (5.4%) and nausea (4.3%).

Adverse events leading to dose interruption of Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy occurred in 73% of patients; the most common adverse reactions (≥2%) leading to dose interruption were vomiting (29.3%), nausea (28.4%) and decreased appetite (3.6%).

The most common adverse reactions (≥2%) leading to dose rate reduction of the Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy infusion were nausea (9.7%) and vomiting (7.8%).

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed in this section by frequency category. Frequency categories are defined as follows: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 4. Adverse reactions

Immune system disorders	
Common	Drug hypersensitivity
Uncommon	Anaphylactic reaction
Metabolism and nutrition disorders	
Very common	Hypoalbuminemia, decreased appetite
Gastrointestinal disorders	
Very common	Vomiting, nausea, abdominal pain upper
Common	Salivary hypersecretion
General disorders and administration site conditions	
Very common	Oedema peripheral
Common	Malaise
Investigations	
Very common	Weight decreased
Injury, poisoning and procedural complications	
Common	Infusion related reaction

Description of selected adverse reactions

Hypersensitivity reactions
In the integrated safety analysis, all grade anaphylactic reaction and drug hypersensitivity occurred in the Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631), 1.6% (10/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.8% (5/611), 1.6% (10/611)]. Severe (Grade 3) anaphylactic reaction and drug hypersensitivity occurred at a similar frequency in the Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631), 0.2% (1/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.3% (2/611), 0.2% (1/611)]. The median time to first onset of anaphylactic reaction or drug hypersensitivity with Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy was 22 days or 113 days, respectively.

Three patients (0.5%) permanently discontinued Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy due to anaphylactic reaction. Dose interruption of Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy was experienced due to drug hypersensitivity in six patients (1.0%). The infusion rate was reduced for

Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy in one patient (0.2%) due to drug hypersensitivity.

Infusion related reaction
In the integrated safety analysis, all grade IRR occurred in the Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 3.2% (20/631) compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm at 1.1% (7/611). Severe (Grade 3) IRRs occurred more frequently in the Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0.5% (3/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [0% (0/611)]. The median time to first onset of infusion-related reaction with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy was 22 days.

An IRR led to permanent discontinuation of Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy in 4 (0.6%) patients and dose interruption in 10 (1.6%) patients. The infusion rate was reduced for Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy in 2 patients (0.3%) due to an IRR.

Nausea and vomiting
In the integrated safety analysis, all grade nausea and vomiting occurred more frequently in the Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy arm [77.2% (487/631), 66.9% (422/631)] compared with the placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arm [58.9% (360/611), 36.8% (225/611)]. Severe (Grade 3) nausea and vomiting in the Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy and placebo in combination with fluoropyrimidine and platinum-containing chemotherapy arms occurred at the following frequencies: nausea [11.6% (73/631) and 4.7% (29/611)] and vomiting [13.6% (86/631) and 4.7% (29/611)]. The median time to first onset of nausea or vomiting with Vyloy in combination with fluoropyrimidine and platinum-containing chemotherapy was 1 day or 1 day, respectively.

Nausea led to permanent discontinuation of Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy in 27 (4.3%) patients and dose interruption in 179 (28.4%) patients. Vomiting led to permanent discontinuation of Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy in 34 (5.4%) patients and dose interruption in 185 (29.3%) patients. The infusion rate was reduced for Vyloy and/or fluoropyrimidine and platinum-containing chemotherapy in 61 patients (9.7%) due to nausea and in 49 patients (7.8%) due to vomiting.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any

suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In case of overdose, the patient should be closely monitored for adverse reactions, and supportive treatment should be administered, as appropriate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies and antibody drug conjugates, other monoclonal antibodies and antibody drug conjugates, ATC code: L01FX31.

Mechanism of action

Zolbetuximab is a chimeric (mouse/human IgG1) monoclonal antibody directed against the tight junction molecule CLDN18.2. Zolbetuximab depletes CLDN18.2-positive cells via antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Cytotoxic drugs were shown to increase CLDN18.2 expression on human cancer cells and to improve zolbetuximab-induced ADCC and CDC activities.

Clinical efficacy and safety

Gastric or GEJ adenocarcinoma

In both the SPOTLIGHT and GLOW studies: CLDN18.2 positivity (defined as ≥75% of tumour cells demonstrating moderate to strong membranous CLDN18 staining) was determined by immunohistochemistry on gastric or GEJ tumour tissue specimens from all patients with the VENTANA CLDN18 (43-14A) RxDx Assay performed in a central laboratory.

SPOTLIGHT (8951-CL-0301)
The safety and efficacy of zolbetuximab in combination with mFOLFOX6 was evaluated in a phase 3, double-blind, randomised, multicentre study that enrolled 565 patients whose tumours were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric or gastro-oesophageal junction (GEJ) adenocarcinoma.

Patients were randomised 1:1 to receive zolbetuximab in combination with mFOLFOX6 (n=283) or placebo in combination with mFOLFOX6 (n=282). Zolbetuximab was administered intravenously at a loading dose of 800 mg/m^2 (Day 1 of cycle 1) followed by a maintenance dose of 600 mg/m^2 every 3 weeks in combination with up to 12 treatments (4 cycles) of mFOLFOX6 (oxaliplatin 85 mg/m^2, folinic acid (leucovorin or local equivalent) 400 mg/m^2, fluorouracil 400 mg/m^2 given as a bolus and fluorouracil 2400 mg/m^2 given as a continuous infusion) administered on Days 1, 15 and 29 of a 42-day cycle. After 12 treatments, patients were allowed to continue treatment with zolbetuximab, 5-fluorouracil and folinic acid (leucovorin or local equivalent) at the discretion of the investigator, until progression of disease or unacceptable toxicity.

Treatment with zolbetuximab continued until RECIST v1.1-defined progression of disease as determined by an independent review committee (IRC) or a subsequent anticancer treatment was initiated. Tumour assessments were performed every 9 weeks up to and including week 54, then every 12 weeks thereafter.

The primary efficacy outcome was Progression Free Survival (PFS) as assessed per RECIST v1.1 by IRC. The key secondary efficacy outcome was Overall Survival (OS).

Table 5 summarises the primary analysis (final PFS, interim OS) baseline characteristics for the SPOTLIGHT study.

Table 5. Baseline characteristics in SPOTLIGHT (primary analysis)

Category	**Zolbetuximab with mFOLFOX6 n=283**	**Placebo with mFOLFOX6 n=282**
Age (years)		
Median age (range)	62 (27 to 83)	60 (20 to 86)
≥18 to ≤64 (%)	60	62
≥65 (%)	40	38
Race (%)		
White	54	53
Asian	37	38
American Indian or Alaskan	3	3
Black or African American	2	1
Other	4	5
Gender (%)		
Male	62	62
Female	38	38
ECOG performance status		
0 (%)	45	41
1 (%)	55	59
Missing data (n)	4	4
Mean Body Surface area (m^2), (range)	1.7 (1.2 to 2.4)	1.7 (1.1 to 2.5)
Median time from diagnosis (days),	56 (2 to 3010)	56 (7 to 5366)

Category	Zolbetuximab with mFOLFOX6 n=283	Placebo with mFOLFOX6 n=282
(range)		
Tumour location		
Distal (%)	39	42
Proximal (%)	37	30
Unknown (%)	24	28
Missing (n)	3	1
Tumour Types		
Diffuse (%)	29	42
Intestinal (%)	25	24
Other (%)	18	15
Mixed (%)	11	5
Unknown (%)	17	14
Missing (n)	1	4

Table 6, Figures 1 and 2 summarise the primary analysis efficacy results for the SPOTLIGHT study.

Table 6. Efficacy Results in SPOTLIGHT (primary analysis)

Endpoint	Zolbetuximab with mFOLFOX6 n=283	Placebo with mFOLFOX6 n=282
Overall survival		
Number (%) of patients with events	149 (52.7)	177 (62.8)
Median in months (95% CI)[a]	18.2 (16.4, 22.9)	15.5 (13.5, 16.5)
Hazard ratio (95% CI)[b,c]	0.750 (0.601, 0.936)	
2-sided p-value[b,d]	0.0107	
12-month OS (%) (95% CI)	67.7 (61.5, 73.1)	60.0 (53.6, 65.7)
18-month OS (%) (95% CI)	50.5 (43.5, 57.0)	38.1 (31.5, 44.5)
24-month OS (%) (95% CI)	38.8 (31.6, 45.9)	28.4 (22.1, 35.0)
Progression Free Survival		
Number (%) of patients with events	146 (51.6)	167 (59.2)
Median in months (95% CI)[a]	10.6 (8.9, 12.5)	8.7 (8.2, 10.3)
Hazard ratio (95% CI)[b,c]	0.751 (0.598, 0.942)	
2-sided p-value[b,d]	0.0132	
12-month PFS (%) (95% CI)	48.9 (41.9, 55.4)	35.0 (28.5, 41.7)
18-month PFS (%) (95% CI)	30.9 (23.8, 38.3)	20.8 (14.5, 28.0)
24-month PFS (%) (95% CI)	24.4 (17.4, 32.1)	14.9 (8.8, 22.5)

a. Based on Kaplan-Meier estimate.
b. Stratification factors were region, number of metastatic sites and prior gastrectomy.
c. Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables.
d. Based on 2-sided log-rank test.

Figure 1. Kaplan Meier Plot of Overall Survival, SPOTLIGHT Study (primary analysis)

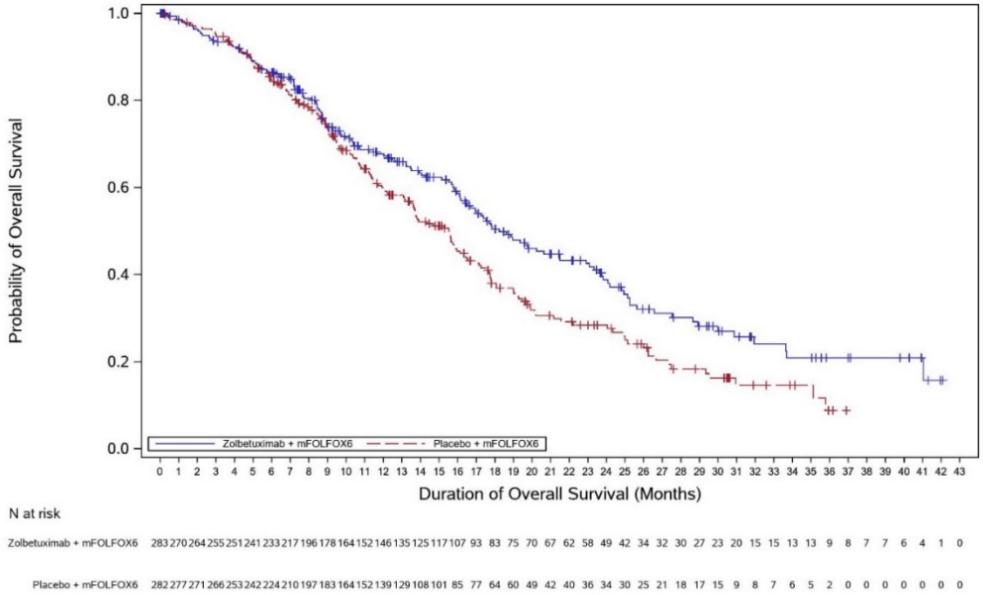
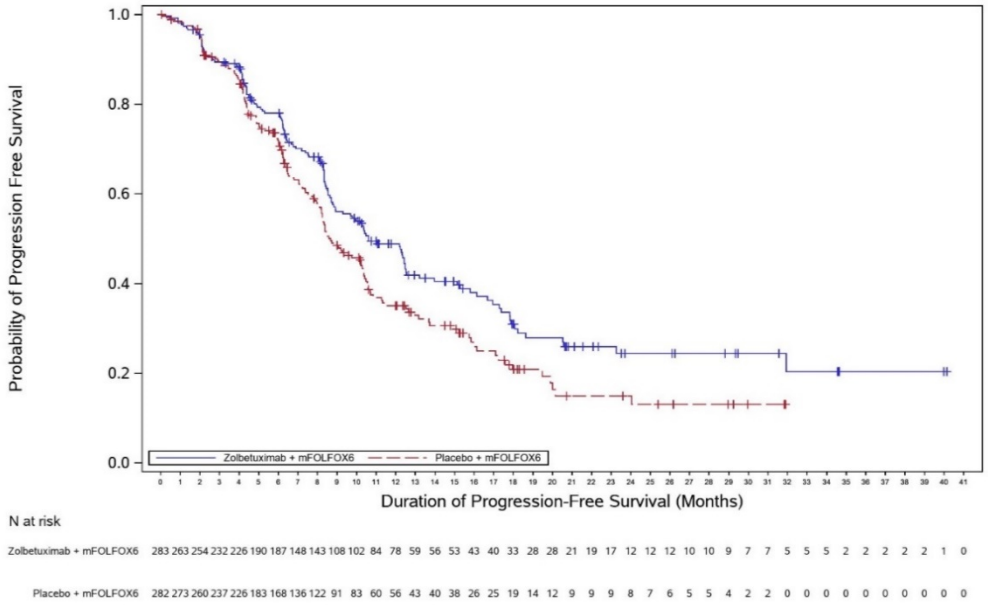


Figure 2. Kaplan Meier Plot of Progression Free Survival, SPOTLIGHT Study (primary analysis)



GLOW (8951-CL-0302)
The safety and efficacy of zolbetuximab in combination with CAPOX was evaluated in a phase 3, double-blind, randomised, multicentre study that enrolled 507 patients whose tumours were CLDN18.2 positive, HER2-negative, with locally advanced unresectable or metastatic gastric or GEJ adenocarcinoma.

Patients were randomised 1:1 to receive zolbetuximab in combination with CAPOX (n=254) or placebo in combination with CAPOX (n=253). Zolbetuximab was administered intravenously at a loading dose of 800 mg/m^2 (Day 1 of cycle 1) followed by a maintenance dose of 600 mg/m^2 every 3 weeks in combination with up

to 8 treatments (8 cycles) of CAPOX administered on Day 1 (oxaliplatin 130 mg/m^2) and on Days 1 to 14 (capecitabine 1000 mg/m^2 twice daily) of a 21-day cycle. After 8 treatments of oxaliplatin, patients were allowed to continue treatment of zolbetuximab and capecitabine at the discretion of the investigator, until progression of disease or unacceptable toxicity.

Conduct of the GLOW study was as for the SPOTLIGHT study.

Table 7 summarises the primary analysis (final PFS, interim OS) baseline characteristics for the GLOW study.

Table 7. Baseline characteristics in GLOW (primary analysis)

Category	**Zolbetuximab with CAPOX n=254**	**Placebo with CAPOX n=253**
Age (years)		
Median age (range)	61 (22 to 82)	59 (21 to 83)
≥18 to ≤64 (%)	66	68
≥65 (%)	34	32
Race (%)		
White	37	36
Asian	63	64
American Indian or Alaskan	0	0
Black or African American	0	0
Other	0	0
Gender (%)		
Male	63	62
Female	37	38
ECOG performance status		
0 (%)	43	43
1 (%)	57	57
Missing data (n)	1	3
Mean Body Surface area (m^2), (range)	1.7 (1.2 to 2.3)	1.7 (1.1 to 2.3)
Median time from diagnosis (days), (range)	44 (12 to 2396)	44 (2 to 6010)
Tumour location		
Distal (%)	39	38
Proximal (%)	35	37
Unknown (%)	26	25
Missing (n)	0	0
Tumour Types		
Diffuse (%)	34	40
Intestinal (%)	14	16
Other (%)	13	11
Mixed (%)	8	8
Unknown (%)	30	25
Missing (n)	1	0

Table 8, Figures 3 and 4 summarises the primary analysis efficacy results for the GLOW study.

Table 8. Efficacy Results in GLOW (primary analysis)

Endpoint	Zolbetuximab with CAPOX n=254	Placebo with CAPOX n=253
Overall survival		
Number (%) of patients with events	144 (56.7)	174 (68.8)
Median in months (95% CI)[a]	14.4 (12.3, 16.5)	12.2 (10.3, 13.7)
Hazard ratio (95% CI)[b,c]	0.771 (0.615, 0.965)	
2-sided p-value[b,d]	0.0236	
12-month OS (%) (95% CI)	57.5 (50.7, 63.8)	50.8 (44.1, 57.1)
18-month OS (%) (95% CI)	38.1 (31.0, 45.2)	28.1 (22.0, 34.7)
24-month OS (%) (95% CI)	28.9 (21.8, 36.5)	17.4 (11.6, 24.1)
Progression Free Survival		
Number (%) of patients with events	137 (53.9)	172 (68.0)
Median in months (95% CI)[a]	8.2 (7.5, 8.8)	6.8 (6.1, 8.1)
Hazard ratio (95% CI)[b,c]	0.687 (0.544, 0.866)	
2-sided p-value[b,d]	0.0014	
12-month PFS (%) (95% CI)	34.9 (27.8, 42.1)	19.1 (13.5, 25.5)
18-month PFS (%) (95% CI)	23.9 (17.1, 31.4)	10.6 (5.7, 17.3)
24-month PFS (%) (95% CI)	14.5 (6.2, 26.2)	7.3 (3.0, 14.2)

a. Based on Kaplan-Meier estimate.
b. Stratification factors were region, number of metastatic sites and prior gastrectomy.
c. Based on Cox proportional hazards model with treatment, region, number of organs with metastatic sites and prior gastrectomy as the explanatory variables.
d. Based on 2-sided log-rank test.

Figure 3. Kaplan Meier Plot of Overall Survival, GLOW Study (primary analysis)

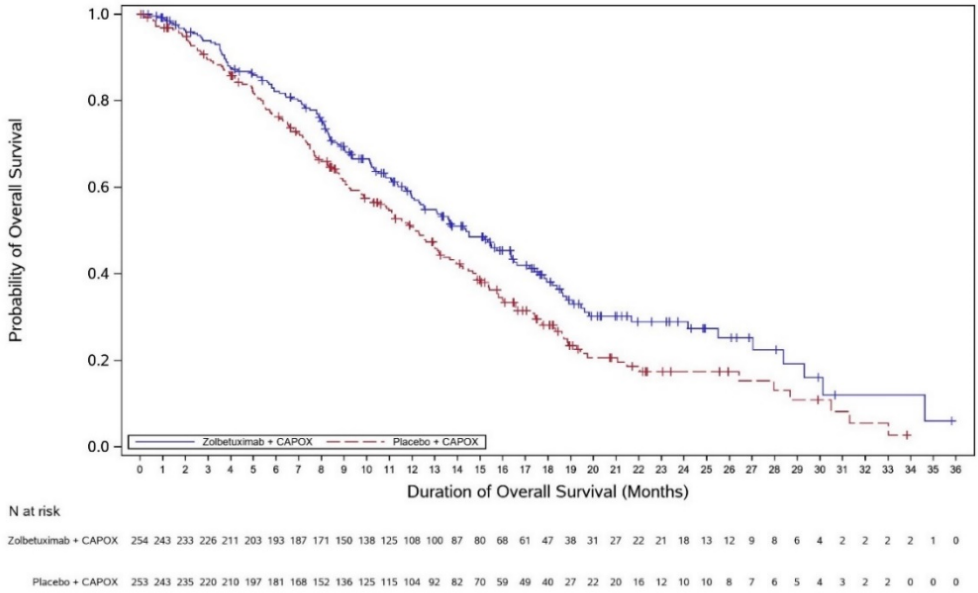
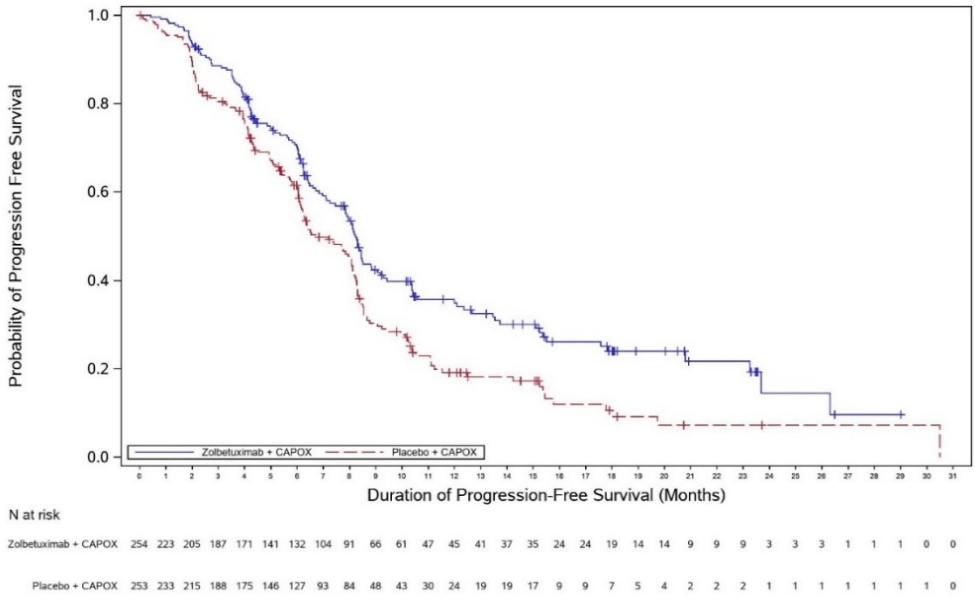


Figure 4. Kaplan Meier Plot of Progression Free Survival, GLOW Study (primary analysis)



5.2 Pharmacokinetic properties

Following intravenous administration, zolbetuximab exhibited dose-proportional pharmacokinetics at doses ranging from 33 mg/m^2 to 1000 mg/m^2. When administered at 800/600 mg/m^2 every 3 weeks, steady state was achieved by 18 weeks with a mean (SD) C_{max} and AUC_{tau} at 425 (91) µg/mL and 3359 (1254) day•µg/mL, respectively.

Distribution

The estimated mean steady state volume of distribution of zolbetuximab was 16.4 L.

Biotransformation

Zolbetuximab is expected to be catabolised into small peptides and amino acids.

Elimination

The estimated mean clearance (CL) and $t_{1/2}$ of zolbetuximab was 0.0150 L/h and 43.6 d, respectively.

Special Populations

Elderly
Population pharmacokinetic analysis indicates that age [range: 22 to 83 years; 32.2% (230/714) were >65 years, 5.0% (36/714) were >75 years] did not have a clinically meaningful effect on the pharmacokinetics of zolbetuximab.

Race and gender
Based on the population pharmacokinetic analysis, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified based on gender [62.3% male, 37.7% female] or race [50.1% White, 42.2% Asian, 4.2% Missing, 2.7% Others, and 0.8% Black].

Renal impairment
Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified in patients with mild [creatinine clearance (CrCL) ≥60 to <90 mL/min; n=298] to moderate (CrCL ≥30 to <60 mL/min; n=109) renal impairment based on CrCL estimated by the Cockcroft-Gault (C-G) formula. Zolbetuximab has only been evaluated in a limited number of patients with severe renal impairment (CrCL ≥15 to <30 mL/min; n=1).

Hepatic impairment
Based on the population pharmacokinetic analysis using data from clinical studies in patients with gastric or GEJ adenocarcinomas, no clinically significant differences in the pharmacokinetics of zolbetuximab were identified in patients with mild hepatic impairment as measured by total bilirubin (TB) and aspartate aminotransferase (AST) (TB ≤ upper limit of normal (ULN) and AST > ULN, or TB > 1 to 1.5 x ULN and any AST; n=108). Zolbetuximab has only been evaluated in a limited number of patients with moderate hepatic impairment (TB > 1.5 to 3 x ULN and any AST; n=4) and has not been evaluated in patients with severe hepatic impairment (TB > 3 to 10 x ULN and any AST).

Drug Interaction Studies

Zolbetuximab is not a cytokine modulator and there are no known effects of its mechanism of action on cytochrome P450 or drug transporters; therefore, no *in vitro* or *in vivo* drug-drug interaction or transporter studies have been conducted.

Based on a phase 2 study, coadministration of zolbetuximab with mFOLFOX6 did not show a clinically meaningful change in drug exposure of zolbetuximab, oxaliplatin, or 5-fluorouracil (5-FU). Therefore, no dose adjustment is required for zolbetuximab and mFOLFOX6 when used in combination.

This finding is also expected to be applicable to CAPOX, which contains oxaliplatin and capecitabine (a prodrug of 5-FU), therefore no dose adjustment is required for zolbetuximab and CAPOX when used in combination.

Immunogenicity

In an approximately 30-month treatment period of 2 clinical studies of zolbetuximab 800/600 mg/m^2 every 3 weeks in combination with mFOLFOX6/CAPOX in patients with locally advanced unresectable or metastatic HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive, the incidence of treatment emergent anti-zolbetuximab antibody formation was 9.5% [46 of 485 total zolbetuximab-treated patients who were tested for anti-drug antibodies (ADAs)].

Because of the low occurrence of ADAs, the effect of these antibodies on the pharmacokinetics, safety and/or effectiveness of zolbetuximab is unknown.

Pharmacokinetic/pharmacodynamic Relationship

Zolbetuximab doses of 800/600 mg/m^2 every 3 weeks were evaluated in clinical studies, with doses of 800/400 mg/m^2 every 2 weeks evaluated using modelling and simulation. The population PK model predicted that 800/400 mg/m^2 every 2 weeks dosing regimen will have about 23% lower C_{max} at steady state and 9.7-21% higher C_{trough} across the treatment period when compared to 800/600 mg/m^2 every 3 weeks dosing regimen. These differences in zolbetuximab exposure are not expected to be clinically meaningful, which are supported by the simulation from the exposure-response model for efficacy and safety, as well as the tumour dynamic model. Based on these assessments, there are no clinically significant differences in efficacy or safety between zolbetuximab doses of 800/600 mg/m^2 every 3 weeks and 800/400 mg/m^2 every 2 weeks in patients with HER2-negative gastric or GEJ adenocarcinoma whose tumours are CLDN18.2 positive (see section 4.2).

5.3 Preclinical safety data

No studies in animals have been performed to evaluate carcinogenicity or mutagenicity. Zolbetuximab is an antibody intended to treat patients with advanced cancer and not expected to interact with DNA.

Preclinical data suggest zolbetuximab binds selectively to cell lines transfected with CLDN18.2 or those that endogenously express CLDN18.2 and reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity.

In an embryo-foetal development toxicity study, where zolbetuximab was administered to pregnant mice during the period of organogenesis at doses up to 300 mg/kg (up to approximately 1.8 times the recommended human dose of 600 mg/m^2, based on AUC), zolbetuximab crossed the placental barrier. The resulting concentration of zolbetuximab in foetal serum at Day 18 of gestation was higher than that in the maternal serum at Day 16 of gestation. The increased concentration of zolbetuximab in foetal serum did not result in any external or visceral foetal abnormalities (malformations or variations).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Arginine
Phosphoric acid
Sucrose

Polysorbate 80

6.2 Incompatibilities

Do not co-administer other medicinal products through the same infusion line.

6.3 Shelf life

Unopened vial

Up to 48 months.

Reconstituted vial

Reconstituted vials may be stored at room temperature (≤30°C) for up to 6 hours. Do not freeze. Do not expose to direct sunlight. Discard unused vials with reconstituted solution beyond the recommended storage time.

Prepared infusion bag

The prepared infusion bag should be administered immediately. If not administered immediately, the prepared infusion bag should be stored:

- under refrigeration at 2°C to 8°C for no longer than 24 hours including infusion time from the end of the preparation of the infusion bag. Do not freeze.
- at room temperature (≤30°C) for no longer than 8 hours including infusion time from when the prepared infusion bag is removed from the refrigerator.

Do not expose to direct sunlight. Discard unused prepared infusion bags beyond the recommended storage time.

6.4 Special precautions for storage

Unopened vials

Store in a refrigerator (2ºC to 8ºC).
Do not freeze.
Store in the original package in order to protect from light.

For storage conditions after reconstitution and dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Clear Type I 50 mL glass vial with European blow-back feature, grey bromobutyl rubber stopper with ethylene tetrafluoroethylene film, 20 mm aluminium seal with a violet cap.

Pack sizes: Cardboard carton containing 1 vial.

6.6 Special precautions for disposal

Instructions for preparation and administration

Reconstitution in single-dose vial

1. Follow procedures for proper handling and disposal of anticancer drugs.
2. Use appropriate aseptic technique for reconstitution and preparation of dosing solutions.
3. Calculate the recommended dose based on the patient's body surface area to determine the number of vials needed.
4. Reconstitute the vial by slowly adding 15.0 mL of Sterile Water For Injection (SWFI). If possible, direct the stream of SWFI along the walls of the vial and not directly onto the lyophilised powder. The reconstituted solution contains 20 mg/mL of zolbetuximab.
5. Slowly swirl each vial until the contents are completely dissolved. Allow the reconstituted vial(s) to settle. Visually inspect the solution until the bubbles are gone. Do not shake the vial.
6. Visually inspect the solution for particulate matter and discolouration. The reconstituted solution should be clear to slightly opalescent, colourless to slight yellow and free of visible particles. Discard any vial with visible particles or discolouration.
7. Based upon the calculated dose amount, the reconstituted solution from the vial(s) should be added to the infusion bag immediately. This product does not contain a preservative. If not used immediately, refer to section 6.3 for storage of reconstituted vials.

Dilution in infusion bag

8. Withdraw the calculated dose amount of reconstituted solution from the vial(s) and transfer into an infusion bag.
9. Dilute zolbetuximab with 0.9% Sodium Chloride for Injection. The infusion bag size should allow enough diluent to achieve a final concentration of 2 mg/mL zolbetuximab.

The diluted dosing solution of zolbetuximab is compatible with intravenous infusion bags composed of polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with either plasticiser [Di-(2-ethylhexyl) phthalate (DEHP) or Trioctyl trimellitate (TOTM)], ethylene propylene copolymer, ethylene-vinyl acetate (EVA) copolymer, polypropylene and styrene-ethylene-butylene-styrene copolymer, or glass (bottle for administration use), and infusion tubing composed of PE, polyurethane (PU), PVC with either plasticiser [DEHP, TOTM or Di(2-ethylhexyl) terephthalate], polybutadiene (PB), or elastomer modified polypropylene with in-line filter membranes (pore size 0.2 μm) composed of polyethersulfone or polysulfone.

10. Mix diluted solution by gentle inversion. Do not shake the bag.
11. Visually inspect the infusion bag for any particulate matter prior to use. The diluted solution should be free of visible particles. Do not use the infusion bag if particulate matter is observed.
12. Discard any unused portion left in the single-dose vials.

Administration

13. Do not co-administer other medicinal products through the same infusion line.
14. Immediately administer the infusion over a minimum of 2 hours through an intravenous line. Do not administer as an IV push or bolus.

No incompatibilities have been observed with closed system transfer device composed of PP, PE, stainless steel, silicone (rubber/oil/resin), polyisoprene, PVC or with plasticiser [TOTM], acrylonitrile-butadiene-styrene (ABS) copolymer, methyl methacrylate-ABS copolymer, thermoplastic elastomer, polytetrafluoroethylene, polycarbonate, polyethersulfone, acrylic copolymer, polybutylene terephthalate, PB, or EVA copolymer.

No incompatibilities have been observed with central port composed of silicone rubber, titanium alloy or PVC with plasticiser [TOTM]. In-line filters (pore size of 0.2 μm with materials listed above) are recommended to be used during administration.

15. If not administered immediately, refer to section 6.3 for storage of the prepared infusion bag.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 00166/0442

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

22/04/2026